PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 July 2001 (05.07.01)	
International application No. PCT/US00/17868	**Applicant's or agent's file reference** 051023/0108
International filing date (day/month/year) 28 July 2000 (28.07.00)	**Priority date** (day/month/year) 28 July 1999 (28.07.99)
Applicant PADIA, Janak et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 February 2001 (26.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

H. Zhou

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
051023/0108		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 17868	28/07/2000	28/07/1999
Applicant		
KIRIN BEER KABUSHIKI KAISHA		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

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6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/[redacted] 00/17868

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/28 C07C275/30 A61K31/17 A61P37/00 C07D213/38
C07D209/16 C07D215/12 C07D307/68 C07D307/52 C07D317/58
C07D333/20 C07D207/09 C07D233/54 C07C323/25 C07C311/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 432 442 A (WARNER LAMBERT CO) 19 June 1991 (1991-06-19) claims 1-5,11-13; example 16 ---	1-10,25
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 02, 30 January 1998 (1998-01-30) -& JP 09 278737 A (TANABE SEIYAKU CO LTD), 28 October 1997 (1997-10-28) original JP-document, page 8, table, compounds 13 and 14 abstract --- -/--	1-10,25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2000	13/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/17868

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/05 C07D257/04 C07C275/42 C07C275/38 C07C323/43
C07D277/66 C07D213/75

According to International Patent Classification (IPC) or to both national classification and IPC

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAZUYA NAKAO ET AL.: "Quantitative Structure-Activity Analyses of Novel Hydroxyphenylurea Derivatives as Antioxidants" BIOOGANIC & MEDICINAL CHEMISTRY, vol. 6, no. 6, 1998, pages 849-868, XP000961127 page 855; examples 43,44; table 2 --- -/--	1-10,25

[X] Further documents are listed in the continuation of box C.

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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna[redacted]al Application No
PC[redacted] 00/17868

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATRICK M. O'BRIEN ET AL.: "Inhibitors of Acyl-CoA: Cholesterol O-Acyl Transferase (ACAT) as Hypocholesterolemic Agents 8. Incorporation of Amide or Amine Functionalities into a Series of Disubstituted Ureas and Carbamates. Effects on ACAT Inhibition in Vitro and Efficacy in Vivo" JOURNAL OF MEDICINAL CHEMISTRY., vol. 37, 1994, pages 1810-1822, XP002153795 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 1812; examples 10A,10B	1-10,25
X	WILLIAM J. ROST ET AL.: "N-Aralkyl-N-methylaminoethyl Carbanilates as Hypocholesteremic Agents" JOURNAL OF PHARMACEUTICAL SCIENCES., vol. 56, no. 12, December 1967 (1967-12), pages 1598-1603, XP002153796 WASHINGTON US page 1602 -page 1603; claims 49-51; table VII	1,2, 5-10,25
X	US 4 880 802 A (RUDOLF SCHOHE ET AL.) 14 November 1989 (1989-11-14) column 59; example 65	1,2, 5-10,25
X	DE 888 699 C (BAYER) 3 September 1953 (1953-09-03) examples 5,8,11	1
A	EP 0 903 349 A (F. HOFFMANN-LA ROCHE) 24 March 1999 (1999-03-24) cited in the application claims; examples	1,25-41

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/[redacted] 00/17868

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0432442 A	19-06-1991	AU 6578090 A	09-05-1991
		CA 2029338 A	07-05-1991
		CN 1051553 A	22-05-1991
		JP 3246257 A	01-11-1991
		NO 904801 A	07-05-1991
		PT 95780 A	30-09-1991
		ZA 9008851 A	29-07-1992
JP 09278737 A	28-10-1997	NONE	
US 4880802 A	14-11-1989	DE 3718317 A	16-06-1988
		AT 89546 T	15-06-1993
		AU 606904 B	21-02-1991
		AU 8241787 A	16-06-1988
		CA 1332834 A	01-11-1994
		CN 87107539 A	13-07-1988
		DD 281376 A	08-08-1990
		DE 3785915 D	24-06-1993
		DK 647087 A	11-06-1988
		EP 0270947 A	15-06-1988
		ES 2054649 T	16-08-1994
		FI 875395 A	11-06-1988
		HU 46654 A	28-11-1988
		JP 1153662 A	15-06-1989
		NO 874939 A,B,	13-06-1988
		NZ 222819 A	28-05-1991
		PH 25491 A	24-07-1991
		PT 86309 A,B	01-01-1988
		US 5463105 A	31-10-1995
		US 5026857 A	25-06-1991
		US 5153225 A	06-10-1992
		US 5298513 A	29-03-1994
		ZA 8709254 A	09-06-1988
DE 888699 C		NONE	
EP 903349 A	24-03-1999	AU 8080098 A	25-02-1999
		BR 9803179 A	28-03-2000
		CA 2245043 A	18-02-1999
		CN 1211572 A	24-03-1999
		CZ 9802566 A	17-03-1999
		DE 19837386 A	25-02-1999
		FR 2767826 A	05-03-1999
		GB 2330580 A	28-04-1999
		HR 980450 A	30-06-1999
		HU 9801887 A	28-06-1999
		IT MI981902 A	18-02-2000
		JP 3014367 B	28-02-2000
		JP 11147872 A	02-06-1999
		NO 983749 A	19-02-1999
		PL 328049 A	01-03-1999
		SG 70110 A	25-01-2000
		ZA 9807448 A	22-01-1999

SHOE 051023/108

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
FOLEY & LARDNER
Attn. BENT, Stephen A.
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109
UNITED STATES OF AMERICA

Date of mailing *(day/month/year)* 13/12/2000	
Applicant's or agent's file reference 051023/0108	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 00/17868	International filing date *(day/month/year)* 28/07/2000
Applicant KIRIN BEER KABUSHIKI KAISHA	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

ACTION DUE: April 19
DOCKETED
RMDB-
L/I- 1/13/01
D/I- 1/30/01
DUE- 2/13/01
By JME
Date 12/19/00
RETURN TO: INT'L ATTY FOR FURTHER A
DRB 12/29

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	John De Bruijn

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the languag of the international application is English, the letter must be in English; if the language of the internati nal application i French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
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International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
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Applicant		
KIRIN BEER KABUSHIKI KAISHA		

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17868

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Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2000	13/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/17868

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/05 C07D257/04 C07C275/42 C07C275/38 C07C323/43
C07D277/66 C07D213/75

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAZUYA NAKAO ET AL.: "Quantitative Structure-Activity Analyses of Novel Hydroxyphenylurea Derivatives as Antioxidants" BIOOGANIC & MEDICINAL CHEMISTRY, vol. 6, no. 6, 1998, pages 849-868, XP000961127 page 855; examples 43,44; table 2 --- -/--	1-10,25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PATRICK M. O'BRIEN ET AL.: "Inhibitors of Acyl-CoA: Cholesterol O-Acyl Transferase (ACAT) as Hypocholesterolemic Agents 8. Incorporation of Amide or Amine Functionalities into a Series of Disubstituted Ureas and Carbamates. Effects on ACAT Inhibition in Vitro and Efficacy in Vivo" JOURNAL OF MEDICINAL CHEMISTRY., vol. 37, 1994, pages 1810-1822, XP002153795 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 1812; examples 10A,10B	1-10,25
X	WILLIAM J. ROST ET AL.: "N-Aralkyl-N-methylaminoethyl Carbanilates as Hypocholesteremic Agents" JOURNAL OF PHARMACEUTICAL SCIENCES., vol. 56, no. 12, December 1967 (1967-12), pages 1598-1603, XP002153796 WASHINGTON US page 1602 -page 1603; claims 49-51; table VII	1,2, 5-10,25
X	US 4 880 802 A (RUDOLF SCHOHE ET AL.) 14 November 1989 (1989-11-14) column 59; example 65	1,2, 5-10,25
X	DE 888 699 C (BAYER) 3 September 1953 (1953-09-03) examples 5,8,11	1
A	EP 0 903 349 A (F. HOFFMANN-LA ROCHE) 24 March 1999 (1999-03-24) cited in the application claims; examples	1,25-41

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 00/17868

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26 - 35 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/17868

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0432442 A	19-06-1991	AU 6578090 A	09-05-1991
		CA 2029338 A	07-05-1991
		CN 1051553 A	22-05-1991
		JP 3246257 A	01-11-1991
		NO 904801 A	07-05-1991
		PT 95780 A	30-09-1991
		ZA 9008851 A	29-07-1992
JP 09278737 A	28-10-1997	NONE	
US 4880802 A	14-11-1989	DE 3718317 A	16-06-1988
		AT 89546 T	15-06-1993
		AU 606904 B	21-02-1991
		AU 8241787 A	16-06-1988
		CA 1332834 A	01-11-1994
		CN 87107539 A	13-07-1988
		DD 281376 A	08-08-1990
		DE 3785915 D	24-06-1993
		DK 647087 A	11-06-1988
		EP 0270947 A	15-06-1988
		ES 2054649 T	16-08-1994
		FI 875395 A	11-06-1988
		HU 46654 A	28-11-1988
		JP 1153662 A	15-06-1989
		NO 874939 A,B,	13-06-1988
		NZ 222819 A	28-05-1991
		PH 25491 A	24-07-1991
		PT 86309 A,B	01-01-1988
		US 5463105 A	31-10-1995
		US 5026857 A	25-06-1991
		US 5153225 A	06-10-1992
		US 5298513 A	29-03-1994
		ZA 8709254 A	09-06-1988
DE 888699 C		NONE	
EP 903349 A	24-03-1999	AU 8080098 A	25-02-1999
		BR 9803179 A	28-03-2000
		CA 2245043 A	18-02-1999
		CN 1211572 A	24-03-1999
		CZ 9802566 A	17-03-1999
		DE 19837386 A	25-02-1999
		FR 2767826 A	05-03-1999
		GB 2330580 A	28-04-1999
		HR 980450 A	30-06-1999
		HU 9801887 A	28-06-1999
		IT MI981902 A	18-02-2000
		JP 3014367 B	28-02-2000
		JP 11147872 A	02-06-1999
		NO 983749 A	19-02-1999
		PL 328049 A	01-03-1999
		SG 70110 A	25-01-2000
		ZA 9807448 A	22-01-1999

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
051023/0108		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/17868	28/07/2000	28/07/1999
International Patent Classification (IPC) or national classification and IPC C07C275/28		
Applicant KIRIN BEER KABUSHIKI KAISHA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/02/2001	12.10.2001
Name and mailing address of the international preliminary examining authority: Europ an Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Seelmann, M Telephone No. +49 89 2399 8335

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/17868

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-100	as originally filed	

Claims, No.:

2-41	as originally filed	
1	with telefax of	09/07/2001

Drawings, sheets:

1/11-11/11	as originally filed	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 26-31,33-35.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 26-31,33-35.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-25,32,36-41
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-25,32,36-41
Industrial applicability (IA)	Yes:	Claims	1-25,32-36-41
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. According to Rule 67.1 (iv), the present authority did not examine claims 26-31 and 33-35 since its subject-matter is directed to a method of treatment of the human or animal body.

1.1 For the assessment of the present claims 26-31 and 33-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item V

Reasoned statement under Article 35.2 with regard to novelty, inventive step or industrial and applicability; citations and explanations supporting such statement

D1 EP 0 432 442 A
D2 JP 09 278 737 A
D3 N. Kazuya et al., Bioorganic & Medicinal Chemistry, 6(6), 849-868 (1998)
D4 P. M. O'Brien et al., J. Med. Chem., 37, 1810-1822 (1994)
D5 W. J. Rost et al., J. Pharma. Sci., 56(12), 1598-1603 (1967)
D6 US 4 880 802 A
D7 DE 888 699 C
D8 EP 0 903 349 A, cited in the application

Novelty - Art. 33(2) PCT

In order to reestablish novelty, the applicant has removed in claim 1 the following options: $I + n = 1$, R_{10} = aryl and Ar not 2-hydroxy-5(lower)alkoxyphenyl, pyrene, chrysene or phenanthrene. These amendments are allowable. Therefore the derivatives according to claims 1-15 and 17-22 and the pharmaceutical composition according to claim 25 can be considered novel versus **D1-D8**.

Inventive step - Art. 33(3) PCT

D8 pertains to cyclic amines useful as modulators of chemokine CCR-3 receptor activity. The closest urea derivative of **D8**, example 9 on page 56, to those of the present demand differs mainly in that the R_1 and R_2 groups defined in the present demand are bonded together. The technical problem to be solved is to provide other CCR-3 receptor antagonists. The solution of the present demand are the derivatives according to claim 1.

Even though the synthesized compounds of formula (1) covered the scope of claim 1, the technical effects were only shown for the examples where R_{10} = H, OH, RCO-OR'; Ar = phenyl non-substituted or substituted by Br, Cl, F, I, OMe, Me, Ac, CN, SMe, NO_2, CO, EtOCO, nBuOCO, CF_3, ϕ, Oϕ, naphthyl; l = 1. In order to be regarded as inventive if use must be made of the argument that the effect of the smallest structural change on activity can not be predicted (i.e. R_1/R_2 linked or not, **D8**), compounds differing **substantially** from the examples can not be claimed as they can not be expected to have the required activity and as such would not be inventive. Accordingly only the present examples and compounds very similar to them can be claimed. No inventive step can therefore be recognized for the subject-matters of claims 16, 32 and 36-41.

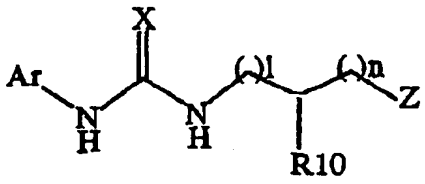
Item VIII

Certain observations on the international application

1. The paragraph on pages 10 (lines 17-20) and 100 (lines 11-17) of the description are relating to the "spirit and scope" of the present demand (Guidelines CIII-4.3a PCT).

2. The expressions and/or terms "and others", "not limited to" and "etc" used throughout the description are indefinite, contravening to the requirements of Art. 6 PCT.

1. A compound having the following Formula:



or a salt, hydrate, or complex thereof, wherein:

l and n are independently 0, 1, 2, 3, 4 or 5;

(l + n) is 2, 3, 4 or 5;

X is O or S;

R10 is selected from the group consisting of hydrogen, hydroxy, C_{3-7}cycloalkyloxy, acyloxy, carboxy, carbamoyl, acyl, amino, alkylamino, arylamino, acylamino, C_{1-5}alkyl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl, alkyloxycarbonyl,

Wherein the C_{1-5}alkyl, aryl, C_{1-5}alkoxy, aryloxy, alkylcarbamoyl, arylcarbamoyl or alkyloxycarbonyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, acyloxy, C_{1-5}alkoxy, aryloxy, heteroaryloxy, nitro, amino, acylamino, alkylamino, arylamino, cyano, aryl, heteroaryl

Wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-5}alkyl or C_{1-5}alkoxy, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydroxy, and halogen;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl,

arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

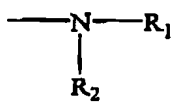
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

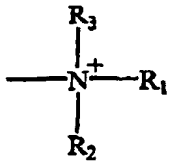
and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

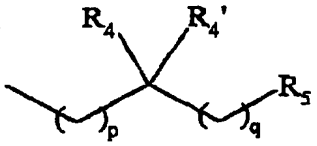
Z is:



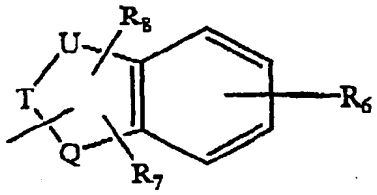
or



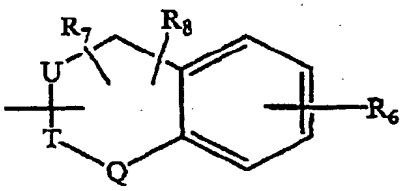
wherein R_1 is:



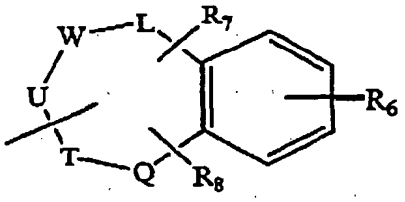
or



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl,

alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds;

R_2 and R_3 are independently selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

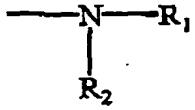
C_{3-7} cycloalkyl

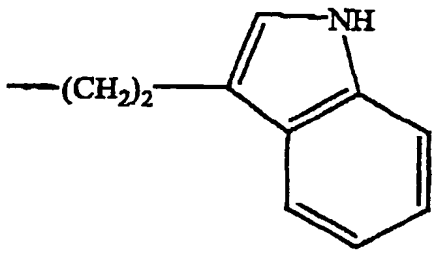
optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that none of R_1, R_2, and R_3 bond together;

further provided that Ar is not 2-hydroxy-5-methoxyphenyl, 2-hydroxy-5-(lower) alkoxyphenyl, pyrene , chrysene, or phenanthrene: and further provided that when Ar is phenyl,

Z is  and R_2 is methyl,



then R_1 is not